AF/1654
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Giorgio ATTARDO et al — Group Art Unit: 1654

Serial No.: 09/976,249 — Examiner: M. V. Meller

Filed: October 15, 2001

For: DIOXOLANE ANALOGS FOR IMPROVED INTER-CELLULAR DELIVERY

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
ALEXANDRIA, VA 22313-1450

Sir:

Further to the Notice of Appeal filed July 28, 2004, attached herewith is Appellants' Brief on Appeal. Pursuant to 37 CFR § 41.20(b)(2), attached is a check for $770 for the filing of this Brief ($340) and for a two month extension of time ($430).

This is an appeal from the decision of the Examiner finally rejecting claims 39, 49 and 51-73.

(1) REAL PARTY IN INTEREST

The application is assigned of record to Shire BioChem Inc., who is the real party in interest herein. The assignment is recorded in Reel 012478/Frame 0492.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

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(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected: 39, 49 and 51-73;

Claims allowed: None;

Claims canceled: 50;

Claims withdrawn: 1-38 and 40-48;

Claims objected to: None;

Claims on Appeal: 39, 49, and 51-73. A copy of the claims on appeal is provided in the attached Claim Appendix.

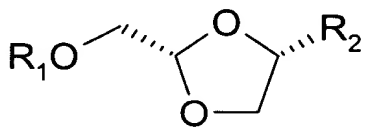
(4) STATUS OF AMENDMENTS AFTER FINAL

No amendments have been submitted subsequent to the Final Rejection in the Office Action of January 26, 2004.

Appellants note that the Advisory Action of August 12, 2004 refers to the denial of entry of amendments. On June 28, 2004 Appellants did file a Reply under 37 CFR §1.116. However, contrary to the implication in the Advisory Action, this Reply did not present any amendments.

(5) SUMMARY OF THE CLAIMED SUBJETC MATTER

Claim 39 is the sole independent claim on appeal. This claim is directed to a genus of dioxolane compounds defined by the formula I:



(I)

wherein R_1 and R_2 are as defined in claim 39 (see the Claim Appendix). These compounds are useful for treating cancer and have lipophillic structures to facilitate their entry into cancer cells. See, e.g., page 10, line 19 - page 14, line 13.

(6) GROUNDS OF REJECTION TO BE REVIWED ON APPEAL

The grounds of rejections that are on Appeal are:

(1) whether claims 39, 49, and 51-73 of the application are unpatentable under 35 U.S.C. §102(b) as being anticipated in view of the disclosure of Belleau et al. (US 5,270,315);

(2) whether claims 39, 49, and 51-73 of the application are unpatentable under 35 U.S.C. §102(b) as being anticipated in view of the disclosure of Belleau et al. (EP 0 337 713);

(3) whether claims 39, 49, and 51-73 of the application are unpatentable under 35 U.S.C. §102(b) as being anticipated in view of the disclosure of Cheng et al. (WO 92/18517);

(4) whether claims 39, 49, and 51-73 of the application are unpatentable under 35 U.S.C. §102(b) as being anticipated in view of the disclosure of "Chu et al.";

(5) whether claims 39, 49, and 51-73 of the application are unpatentable under 35 U.S.C. §102(e) as being anticipated in view of the disclosure of Belleau et al. (US 6,530,753);

(6) whether claims 39, 49, and 51-73 of the application are unpatentable under 35 U.S.C. §102(e) as being anticipated in view of the disclosure of Cimpoia et al. (US 6,541,625); and

(7) whether claims 39, 49, and 51-73 of the application are unpatentable under 35 U.S.C. §102(a) as being anticipated in view of the disclosure of Gourdeau et al. (WO 00/57861).

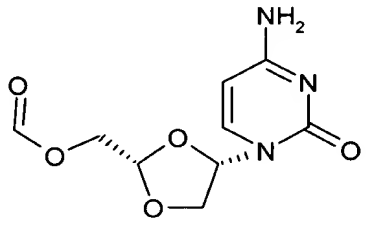
In the Office Actions, the rejections under §102(b) refer to "Chu et al.," but do not state which Chu et al. document is being relied on. There are two Chu et al. documents of record, i.e. WO 96/07413 and US 5,817,667. Appellants' have requested clarification, but have not yet received any such clarification from the Examiner. For the sake of completeness, Appellants' remarks below address both of the Chu et al. references.

Also, in the Office Actions, the rejections under §102(e) refer to Belleau et al. '753 twice. Appellants have assumed that this was a typographical error and that only one "Belleau et al." reference is being applied under §102(e), i.e., US 6,530,753.

(7) APPELLANTS' ARGUMENTS

A. Rejection Under 35 USC §102: Generally

In response to the election of species requirement presented in the Office Action of February 27, 2003, Appellants' elected compound #21 set forth at page 21. In response to Appellants' election, the Examiner indicated that the subject matter examined was that which was characterized as the "core structure," defined by the following structural formula:



The "core structure" encompasses compounds that do not fall within the literal scope of Appellants' claim 39. Thus, merely asserting that a reference anticipates the "core structure" does not result in a conclusion that claim 39 is allegedly anticipated. In other words, an assertion that a reference anticipates the "compound of the core structure" in no way establishes anticipation of Appellants' claimed invention.

In response to the various anticipation rejections, the Appellants argued, among other things, that the rejections did not point where each and every feature of the claimed invention was described in the allegedly anticipatory references. In responding to Appellants' arguments, the Examiner still did not specify relevant portions of the disclosures, but instead, responded that the asserted anticipatory references "clearly showed chemical structures which read on the elected core structure, it was apparent which structure the examiner was referring to." See the Office Action of January 28, 2004. Appellants respectfully submit that this is not the case.

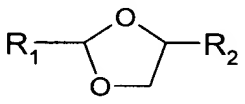
Firstly, many of the structural formulas presented in the prior art references represent

generic formulas which encompass vast numbers of compounds and thus do not "describe" a compound of Appellants' claimed invention in accordance with 35 USC §102. See, e.g., *In re Ruschig et al.*, 154 USPQ 118 (CCPA 1967). See, e.g., formula L at columns 3-4 of Belleau et al. (US '315). Alternatively, many of the structural formulas represent specific compounds which do not fall within the literal scope of claim 39 and in most cases do not have the asserted "core structure."

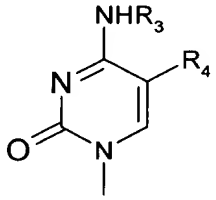
B. Rejection Under 35 USC §102(b)

1. Belleau et al. (US '315)

In the Advisory Action, the Examiner asserts that the so-called core structure is shown under the Summary of the Invention (Column 3, line 28-column 4, line 37). This portion of the disclosure of US '315 describes a Formula L:



R_1 is H, an aliphatic acyl radical from 2 to 16 carbon atoms, a benzoyl which may be substituted in any position by a halogen, a lower alkyl, a lower alkoxy, nitro or trifluoromethyl groups. R_2 can be, inter alia, the heterocyclic radical



R_3 and R_4 are respectively selected from H and a lower alkyl radical having from 1 to 3 carbon atoms, and R_4 may also be an alkenyl radical.

Firstly, it is noted that formula L describes a genus encompassing a large number of compounds. The disclosure of such a genus, in and of itself, does not anticipate each of the compounds falling within the genus. See, e.g., *In re Ruschig et al.*, 154 USPQ 118 (CCPA). Secondly, merely pointing out formula L of US '315 does not demonstrate how this formula describes or even suggests a compound in accordance with Appellants' claim 39. Compare the

definitions of R_1 and R_3 in US '315 and the definitions of R_1, R_3, and R_4 and the proviso clauses of Appellants' claim 39.

The examples in US '315 disclose the following nucleoside analogue compounds: 2-chloromethyl-4-(thymin-1'-yl)-1,3-dioxolane, 2-acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, 2-hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, 2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane, and trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane, 2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolane, 2-hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolane, 2-benzoyloxymethyl-4-(2'-amino-6'-chloro-(purin-9'-yl)-1,3-dioxolane, cis and trans 2-hydroxymethyl-4-(2'-amino-6'-chloro-(purin-9'-yl)-1,3-dioxolane, cis and trans 2-hydroxymethyl-4-(2'-amino-purin-9'-yl)-1,3-dioxolane, cis and trans 2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxolane, and 2-hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolane.

These compounds do not anticipate Appellants' claimed invention. See, e.g., the proviso clauses of claim 39.

In view of the above remarks, it is respectfully submitted that Belleau et al. (US '315) fails to anticipate Appellants' claimed invention. Reversal of the rejection under 35 USC §102(b) in view of Belleau et al. (US '315) is respectfully requested.

2. Belleau et al. (EP 0 337 713)

The entirety of the Examiner's arguments concerning the rejection under 35 USC §102(b) in view of Belleau et al. (EP 0 337 713) is as follows:

Office Action June 3, 2003:

> "The compound of the core structure is anticipated by the references."

Office Action January 28, 2004:

> "The compound of the core structure is anticipated by the references.
>
> Applicant suggests that the examiner didn't point out in the reference where the claimed compound was but since the reference clearly showed chemical structures which read on the elected core structure, it was apparent which structure the examiner was referring to."

The rejection clearly fails to set forth where within the asserted document there is "described," in accordance with 35 USC §102, an embodiment within the scope of Appellants'

claimed invention. In making an anticipation rejection, an examiner must show where each and every feature of the claimed invention is described in the allegedly anticipatory reference. See, e.g., *Ex parte Levy*, 17 USPQ2d 1461, 1462 (BOPA 1990) ["Moreover, it is incumbent upon the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference. "] The rejection does not satisfy this requirement and should be reversed on this basis alone.

The Examiner's assertion in the Office Action of January 28, 2004, that it was apparent which structure was referring being to, does not satisfy the requirement set forth in *Levy*. Moreover, Appellants respectfully submit that this is not the case. Firstly, many of the structural formulas presented in the reference are generic formulas which encompass large number of compounds and thus do not "describe" a compound of Appellants' claimed invention in accordance with 35 USC §102. *Ruschig et al.* See, e.g., formula L at pages 4-5 of EP '713 (which is the same as formula L of US '315 discussed above). Alternatively, many of the structural formulas represent specific compounds which do not fall within the literal scope of claim 39 and in most cases do not have the asserted "core structure." See, e.g., the formulas at page 8-9 of EP '713.

The examples in EP '713 disclose the following nucleoside analogue compounds: 2-chloromethyl-4-(thymin-1'-yl)-1,3-dioxolane, 2-acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, 2-hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, 2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane, and trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane, 2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolane, 2-hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolane, 2-benzoyloxymethyl-4-(2'-amino-6'-chloro-(purin-9'-yl)-1,3-dioxolane, cis and trans 2-hydroxymethyl-4-(2'-amino-6'-chloro-(purin-9'-yl)-1,3-dioxolane, cis and trans 2-hydroxymethyl-4-(2'-amino-purin-9'-yl)-1,3-dioxolane, cis and trans 2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxolane, and 2-hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolane.

These compounds do not anticipate Appellants' claimed invention. See, e.g., the proviso clauses of claim 39.

In view of the above remarks, it is respectfully submitted that Belleau et al. (EP '713) fails to anticipate Appellants' claimed invention. Reversal of the rejection under 35 USC §102(b) in view of Belleau et al. (EP '713) is respectfully requested.

3. Cheng et al. (WO 92/18517)

The entirety of the Examiner's arguments concerning the rejection under 35 USC §102(b) in view of Cheng et al. (WO 92/18517) is as follows:

Office Action June 3, 2003:

> "The compound of the core structure is anticipated by the references."

Office Action January 28, 2004:

> "The compound of the core structure is anticipated by the references.
>
> Applicant suggests that the examiner didn't point out in the reference where the claimed compound was but since the reference clearly showed chemical structures which read on the elected core structure, it was apparent which structure the examiner was referring to."

Advisory Action of

The rejection clearly fails to set forth where within the asserted document there is "described," in accordance with 35 USC §102, an embodiment within the scope of Appellants' claimed invention. See, e.g., *Ex parte Levy*. The rejection does not satisfy this requirement and should be reversed on this basis alone.

The Examiner's assertion in the Office Action of January 28, 2004, that it was apparent which structure was referring being to, does not satisfy the requirement set forth in *Levy*. Moreover, Appellants respectfully submit that this is not the case. WO '517 discloses certain specific compounds and their anti-HBV activity. See, e.g., the structural formulas disclosed at pages 5-6, 8, 15 (middle of the page), 17, page 32, 38, 44, and 48. These compounds do not exhibit a dioxolane ring and thus clearly do not anticipate Appellants' claimed invention. See, for example, the compound depicted at pages 7, 9, and 15 (bottom). This compound exhibits a HO-CH_2- group attached at the 2-position. Compare Appellants' group R_1O- CH_2- and the proviso clause in claim 39.

In view of the above remarks, it is respectfully submitted that Cheng et al. (WO '517) fails to anticipate Appellants' claimed invention. Reversal of the rejection under 35 USC §102(b) in view of Cheng et al. (WO '517) is respectfully requested.

4. Chu et al.

The entirety of the Examiner's arguments concerning the rejection under 35 USC

§102(b) in view of Chu et al. is as follows:

Office Action June 3, 2003:

"The compound of the core structure is anticipated by the references."

Office Action January 28, 2004:

"The compound of the core structure is anticipated by the references. Applicant suggests that the examiner didn't point out in the reference where the claimed compound was but since the reference clearly showed chemical structures which read on the elected core structure, it was apparent which structure the examiner was referring to."

Advisory Action of August 12, 2004:

"in Chu et al., at the top of col. 5 core structure is shown."

Chu et al. (US 5,817,667) discloses the use of (-)-OddC, i.e., (-)-(2S,4S)-1-(2-hydroxymethyl-1,3-dioxolane-4-yl)cytosine, and derivatives thereof, for the treatment of cancer. See, e.g., column 4, line 25-column 5, line 34. The structure shown at the top of column 5 is a generic structure encompassing a vast number of compounds. Such disclosure of a genus of compounds does not describe a compound of Appellants' claimed invention in accordance with 35 USC §102. *Ruschig et al.*

The specific compounds disclosed by US '667 are (-)-(2S,4S)-1-(2-(benzoyloxy)-1,3-dioxolan-4-yl)cytosine, (+)-(2S,4R)-1-(2-(benzoyloxy)-1,3-dioxolan-4-yl)cytosine, and (-)-(2S,4S)-1-(2-hydroxymethyl-1,3-dioxolane-4-yl)cytosine. See Examples 7-8. The compounds described in US '667 do not anticipate Appellants' claimed invention. See, e.g., the proviso clauses of claim 39.

Similar to US '667, Chu et al. (WO 96/07413) discloses the use of (-)-OddC, i.e., (-)-(2S,4S)-1-(2-hydroxymethyl-1,3-dioxolane-4-yl)cytosine, and derivatives thereof, for the treatment of tumors. See, e.g., page 5, line 17-27, page 7, lines 1-11, and page 12, lines 8-28. The specific compounds disclosed by WO '413 are (-)-(2S,4S)-1-(2-(benzoyloxy)-1,3-dioxolan-4-yl)cytosine, (+)-(2S,4R)-1-(2-(benzoyloxy)-1,3-dioxolan-4-yl)cytosine, and (-)-(2S,4S)-1-(2-hydroxymethyl-1,3-dioxolane-4-yl)cytosine. See Examples 7-8. The compounds described in WO '413 do not anticipate Appellants' claimed invention. See, e.g., the proviso clauses of claim 39.

In view of the above remarks, it is respectfully submitted that Chu et al. (US '667 or WO '413) fails to anticipate Appellants' claimed invention. Reversal of the rejection under 35 USC §102(b) in view of Chu et al. (US '667 or WO '413) is respectfully requested.

5. Claims 51 and 54

Claims 51 and 54 recite compounds of the genus defined by claim 39 in which at least one of R_1, R_3 or R_4 contains a heterocyclic group. None of the prior art references cited in the rejection under 35 USC §102(b) describe a compound having a structure containing a heterocyclic group in any of the same positions as appellants' R_1, R_3 and R_4 groups. Reversal of the rejections under 35 USC §102(b) with respect to claims 51 and 54 is respectfully requested.

6. Claims 55 -61

Claims 55-64 each recite specific compounds of the genus defined by claim 39 or small subgenera of the genus defined by claim 39. None of the arguments presented within the rejections under 35 USC §102(b) presented in the Office Actions provides any indication that the allegedly anticipatory references describe any of these specific compounds or a compound falling within the claimed small subgenera. None of the prior art references cited in the rejection under 35 USC §102(b) describe a compound in accordance with any of these claims. Reversal of the rejections under 35 USC §102(b) with respect to claims 55-61 is respectfully requested.

C. Rejection Under 35 USC §102(e)

1. Belleau et al. (US 6,530,753)

The entirety of the Examiner's arguments concerning the rejection under 35 USC §102(e) in view of Belleau et al. (US '753) is as follows:

Office Action June 3, 2003:

"The compound of the core structure is anticipated by the references."

Office Action January 28, 2004:

"The compound of the core structure is anticipated by the references.

Applicant suggests that the examiner didn't point out in the reference where the claimed compound was but since the reference clearly showed chemical structures which read on the elected core structure, it was apparent which structure the examiner was referring to."

Advisory Action of August 12, 2004:

"Belleau et al. '753, example 27 clearly shows the core structure."

As noted above, the "core structure" encompasses compounds that do not fall within the literal scope of Appellants' claim 39. Thus, merely asserting that a compound has the "core structure" does not result in a conclusion that claim 39 is anticipated. An assertion that a reference anticipates the "core structure" in no way establishes anticipation of Appellants' claimed invention.

Example 27 of US '753 discloses the compound 2-benzoyloxymethyl-4-(cytosine-1'-yl)-1,3-dioxolane. This compound does not anticipate Appellants' claim 39. See, e.g., the proviso clauses of claim 39.

Many of the structural formulas presented in the prior art reference represent generic formulas which encompass vast numbers of compounds and thus do not "describe" a compound of Appellants' claimed invention in accordance with 35 USC §102. See, e.g., *In re Ruschig et al.* See, e.g., formulas I, II, and III at column 4 of Belleau et al. (US '753). Alternatively, many of the structural formulas represent specific compounds which do not fall within the literal scope of claim 39 and in most cases do not have the asserted "core structure." See, e.g., the formulas in scheme 1 of Belleau et al. (US '753).

In terms of specific dioxolane nucleoside compounds, US '753 discloses the compounds the following compounds at column 11, line34-column 12, line 8: cis-2-acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, trans-2-acetoxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, and mixtures thereof; cis-2-hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, trans-2-hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, and mixtures thereof; cis-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane, trans-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3 dioxolane, and mixtures thereof; cis-2-hydroxymethyl-4-(cytosin-1-yl)-1,3-dioxolane, trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dioxolane, and mixtures thereof; cis-2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolane, trans-2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-dioxolane, and mixtures

thereof; cis-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolane, trans-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-dioxolane, and mixtures thereof; cis-2-benzoyloxylmethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane, trans-2-benzoyloxylmethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane , and mixtures thereof; cis-2-hydroxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane, trans-2-hydroxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-dioxolane, and mixtures thereof; cis-2-hydroxymethyl-4-(2'-amino-purin-9'-yl)-1,3-dioxolane, trans-2-hydroxymethyl-4-(2'-amino-purin-9'-yl)-1,3-dioxolane, and mixtures thereof; cis-2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxolane, trans-2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-dioxolane, and mixtures thereof; cis-2-hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolane, trans-2-hydroxymethyl-4-(guanin-9'-yl)-1,3-dioxolane, and mixtures thereof; cis-2-hydroxymethyl-5-(N,N-dimethylamino methylene cytosin-1'-yl)-1,3-dioxolane, trans-2-hydroxymethyl-4-(N,N-dimethylamino methylene cytosin-1'-yl)-1,3-dioxolane, and mixtures thereof.

See also the compounds disclosed in the reaction schemes and the Examples. These compounds described by US '753 do not anticipate Appellants' claimed invention.

In view of the above remarks, it is respectfully submitted that Belleau et al. (US '753) fails to anticipate Appellants' claimed invention. Reversal of the rejection under 35 USC §102(e) in view of Belleau et al. (US '753) is respectfully requested.

2. Cimpoia et al. (US 6,541,625)

The entirety of the Examiner's arguments concerning the rejection under 35 USC §102(e) in view Cimpoia et al. (US '625) is as follows:

Office Action June 3, 2003:

> "The compound of the core structure is anticipated by the references."

Office Action January 28, 2004:

> "The compound of the core structure is anticipated by the references.
>
> Applicant suggests that the examiner didn't point out in the reference where the claimed compound was but since the reference clearly showed chemical structures which read on the elected core structure, it was apparent which structure the examiner was referring to."

Advisory Action of August 12, 2004:

"In Cimpoia et al. '753, example 16 clearly shows the core structure."

Example 16 of US '625 discloses the compound 2(S)-benzoyloxymethyl-1,3-dioxolan-4-(S)-yl)-2-oxo-4-amino-pyrimidine. This compound does not anticipate Appellants' claim 39. See, e.g., the proviso clauses of claim 39.

In terms of specific dioxolane nucleoside analogues, Cimpoia et al. (US '652) discloses in the Examples 15-17, and 23-34 the following compounds: 2-(S)-Benzoyloxymethyl-1,3-dioxolan-4-(S)-yl)-2-oxo-4-aminoacetyl-pyrimidine; 2-(S)-Benzoyloxymethyl-1,3-dioxolan-4-(S)-yl)-2-oxo-4-amino-pyrimidine; 2-(S)-hydroxymethyl-1,3-dioxolan-4-(S)-yl)-2-oxo-4-amino-pyrimidine; 9-(2-(R)-benzoyloxymethyl-1,3-dioxolan-4-yl)-6-chloro-2-amino purine; 9-(2-(R)-benzoyloxymethyl-1,3-dioxolan-4-yl)-6-iodo-2-amino purine; 9-(2-(R)-benzoyloxymethyl-1,3-dioxolan-4-yl)-6-(N-cyclopropyl)amino-2-amino purine; 9-(2-(R)-hydroxymethyl-1,3-dioxolan-4-yl)-6-(N-cyclopropyl)amino-2-amino purine; 9-(2-(R)-hydroxymethyl-1,3-dioxolan-4-yl-6-(N-2-cyclopropyl-2-aminomethoxy l)-2-amino purine; 9-(2-(S)-hydroxymethyl-1,3-dioxolan-4-yl)-2-amino purine; 9-(2-(S) hydroxymethyl-1,3-dioxolan-4-yl)-6-amino purine; 9-(2-(S) hydroxymethyl-1,3-dioxolan-4-yl)-6,2-diamino purine; 9-(2-(S) hydroxymethyl-1,3-dioxolan-4-yl)-6-oxo-2-amino purine; 9-(2-(S) hydroxymethyl-1,3-dioxolan-4-yl)-2-oxo-4-amino-5-methyl pyrimidine; 9-(2-(S) hydroxymethyl-1,3-dioxolan-4-yl)-2-oxo-4-amino-5-fluoro pyrimidine; 9-(2-(S) hydroxymethyl-1,3-dioxolan-4-yl)-2,4-dioxo pyrimidine; and 9-(2-(S) hydroxymethyl-1,3-dioxolan-4-yl)-2,4-dioxo-5-methyl pyrimidine.

These compounds described by US '625 do not anticipate Appellants' claimed invention. See, e.g., the proviso clauses of claim 39.

In view of the above remarks, it is respectfully submitted that Cimpoia et al. (US '625) fails to anticipate Appellants' claimed invention. Reversal of the rejection under 35 USC §102(e) in view of Cimpoia et al. (US '625) is respectfully requested.

3. Claims 51 and 54

Claims 51 and 54 recite compounds of the genus defined by claim 39 in which at least one of R_1, R_3 or R_4 contains a heterocyclic group. None of the prior art references cited in the

rejection under 35 USC §102(e) describe a compound having a structure containing a heterocyclic group in any of the same positions as appellants' R_1, R_3 and R_4 groups. Reversal of the rejections under 35 USC §102(e) with respect to claims 51 and 54 is respectfully requested.

4. Claims 55 -61

Claims 55-64 each recite specific compounds of the genus defined by claim 39 or small subgenera of the genus defined by claim 39. None of the arguments presented within the rejections under 35 USC §102(e) presented in the Office Actions provides any indication that the allegedly anticipatory references describe any of these specific compounds or a compound falling within the claimed small subgenera. None of the prior art references cited in the rejection under 35 USC §102(e) describe a compound in accordance with any of these claims. Reversal of the rejections under 35 USC §102(e) with respect to claims 55-61 is respectfully requested.

D. Rejection Under 35 USC §102(a)

1. Gourdeau et al. (WO 00/57861)

The entirety of the Examiner's arguments concerning the rejection under 35 USC §102(b) in view of Gourdeau et al. (WO 00/57861) is as follows:

Office Action June 3, 2003:

> "The compound of the core structure is anticipated by the references."

Office Action January 28, 2004:

> "The compound of the core structure is anticipated by the references.
> Applicant suggests that the examiner didn't point out in the reference where the claimed compound was but since the reference clearly showed chemical structures which read on the elected core structure, it was apparent which structure the examiner was referring to."

The rejection clearly fails to set forth where within the asserted document there is "described," in accordance with 35 USC §102, an embodiment within the scope of Appellants'

claimed invention. See, e.g., *Ex parte Levy*. The rejection should be reversed on this basis alone.

In the Office Action of January 28, 2004, it is argued that "since the reference clearly showed chemical structures which read on the elected core structure, it was apparent which structure the examiner was referring to." Appellants respectfully submit that this is not the case. The only structural formulas presented in WO '861 represent generic formulas which encompass vast numbers of compounds and thus do not "describe" a compound of Appellants' claimed invention in accordance with 35 USC §102. See, e.g., *In re Ruschig et al.*. See, e.g., formula I at page 4, page 6 and page 23 of WO '861.

Furthermore, with respect to the specific compounds, WO '861 discloses the compounds β-L-5'-benzyl- 2'-deoxy-3'-oxa-N-4-acetyl-cytidine, β-L-5'-benzyloxy- 2'-deoxy-3'-oxacytidine and β-L-OddC. See compounds #2, #3 and β-L-OddC at page 18. These compounds do not anticipate Appellants' claimed invention. See, e.g., the proviso clauses of claim 39.

In view of the above remarks, it is respectfully submitted that Gourdeau et al. (WO 861) fails to anticipate Appellants' claimed invention. Reversal of the rejection under 35 USC §102(e) in view of Gourdeau et al. (WO 861) is respectfully requested.

2. Claims 51 and 54

Claims 51 and 54 recite compounds of the genus defined by claim 39 in which at least one of R_1, R_3 or R_4 contains a heterocyclic group. The prior art reference cited in the rejection under 35 USC §102(a) does not describe a compound having a structure containing a heterocyclic group in any of the same positions as appellants' R_1, R_3 and R_4 groups. Reversal of the rejections under 35 USC §102(a) with respect to claims 51 and 54 is respectfully requested.

3. Claims 55 -61

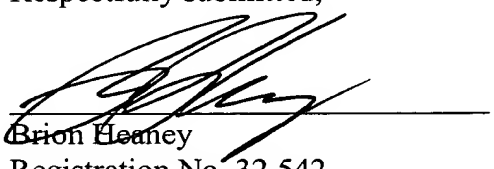
Claims 55-64 each recite specific compounds of the genus defined by claim 39 or small subgenera of the genus defined by claim 39. None of the arguments presented within the rejection under 35 USC §102(a) presented in the Office Actions provides any indication that the allegedly anticipatory reference describes any of these specific compounds or a

compound falling within the claimed small subgenera. The prior art reference cited in the rejection under 35 USC §102(a) does not describe a compound in accordance with any of these claims. Reversal of the rejections under 35 USC §102(a) with respect to claims 55-61 is respectfully requested.

(8) CONCLUSION

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims 39, 49, 51-73, is in error and should be reversed.

Respectfully submitted,



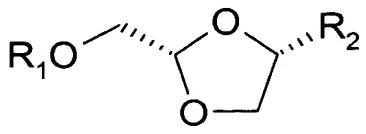
Brion Heaney
Registration No. 32,542

Filed: October 27, 2004

CLAIMS APPENDIX

Claims 1-38 (Withdrawn)

39. (Previously Presented): A compound having the following formula:



(I)

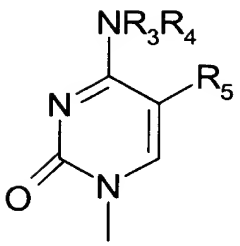
wherein:

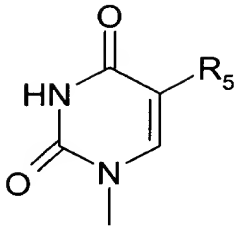
R_1 is H; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $C(O)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof, wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Met, Cys, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

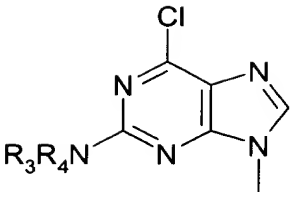
R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

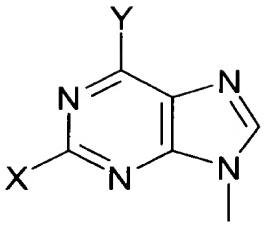
R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

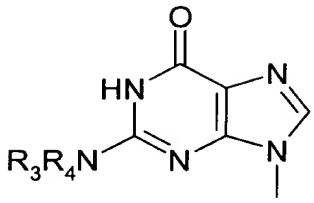
R_2 is











R_3 and R_4 are in each case independently H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{6-24} aryl-C_{1-24}-alkyl; C_{6-24}-aryl-C_{2-24}-alkenyl; C_{5-18} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R_6; -C(O)OR_6; -C(O)NHR_6; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by -R_7;

R_3 and R_4 together can also be =CH-N(C_{1-4}-alkyl)$_2$;

R_5 is H;

R_6 is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-20} alkyl-C_{6-10} aryl, C_{0-20} alkyl-C_{5-10} heteroaromatic ring, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-24} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S; and

R_7 is, in each case, C_{3-20} nonaromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$; or

a pharmaceutically acceptable salt thereof;

with the proviso that at least one of R_1, R_3 and R_4 is

C_{7-24} alkyl;

C_{7-24} alkenyl;

C_{6-24} aryl;

C_{5-20} heteroaromatic ring;

C_{4-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S;

$C(O)R_6$ in which R_6 is C_{4-20} C_{7-24} alkyl, C_{7-24} alkenyl, C_{0-24} alkyl-C_{6-24} aryl, C_{0-24} alkyl-C_{5-20} heteroaromatic ring, C_{3-20}non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S ;

$-C(O)OR_6$ in which R_6 is C_{7-24} alkyl, C_{7-24} alkenyl, C_{0-24} alkyl-C_{6-24} aryl, C_{0-24} alkyl-C_{5-20} heteroaromatic ring, C_{3-20}non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S; or

a dipeptide or tripeptide or mimetic thereof where the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which is optionally terminated by $-R_7$; and

wherein said compound is not 1-[2-benzoyloxymethyl-1,3-dioxolan-4-yl]cytosine.

Claims 40-48 (Withdrawn)

49. (Previously Presented): A compound according to claim 39, wherein if R_3 and R_4 are both H and R_1 is $-C(O)R_6$, $-C(O)OR_6$ or $-C(O)NHR_6$, then R_6 is other than H.

50. (Cancelled):

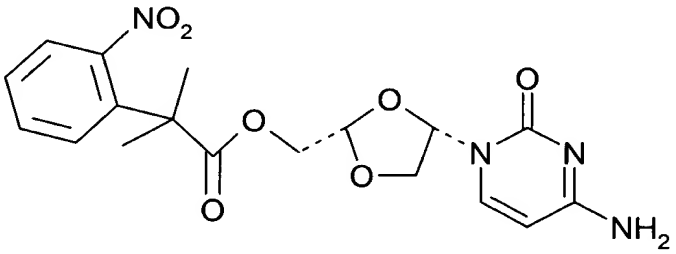
51. (Previously Presented): A compound according to claim 39, wherein at least one of R_1, R_3, or R_4 is piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, adamantyl or quinuclidinyl.

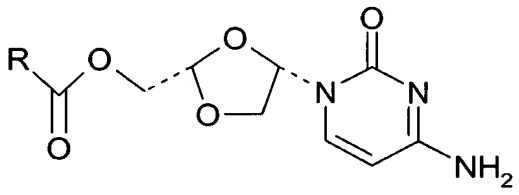
52. (Previously Presented): A compound according to claim 39, wherein at least one of R_1, R_3 or R_4 is acetyl, propionyl, butyryl, valeryl, caprioic, caprylic, capric, lauric, myristic, palmitic, stearic, oleic, linoleic, or linolenic.

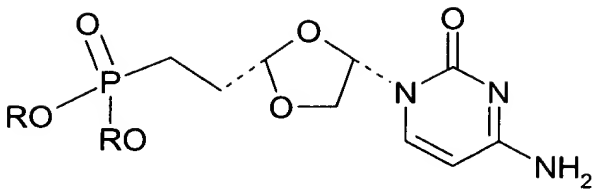
53. (Previously Presented): A compound according to claim 39, wherein at least one of R_1, R_3 or R_4 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, napthyl or biphenyl.

54. (Previously Presented): A compound according to claim 39, wherein at least one of R_1, R_3 or R_4 contains a heterocyclic group selected from the following group: furyl, thiophenyl, pyrrolyl, imidazolyl, pyrazoyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, thiopyranyl, pyrazinyl, benzofuryl, benzothiophenyl, indolyl, benzimidazolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, quinolinyl, isoquinolinyl, carbazolyl, acridinyl, cinnolinyl and quinazolinyl.

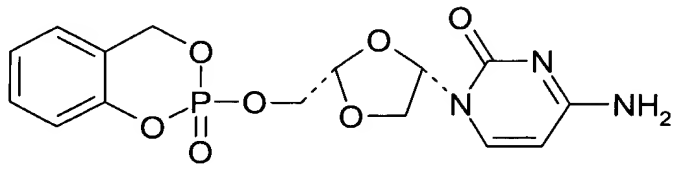
55. (Previously Presented): A compound according to claim 39, wherein the compound is of the formulas



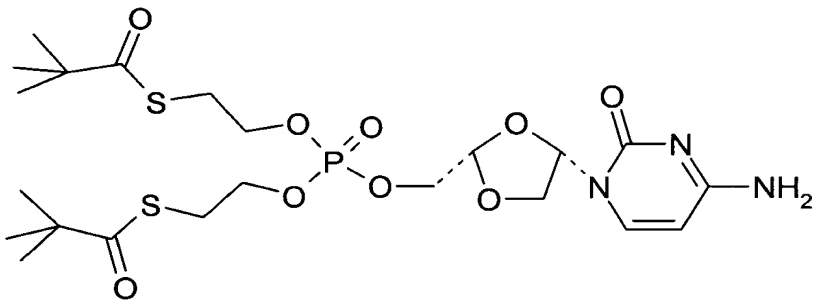




56. (Previously Presented): A compound according to claim 39, wherein the compound is of the formula



57. (Previously Presented): A compound according to claim 39, wherein the compound is of the formula



58. (Previously Presented): A compound according to claim 39, wherein said compound is selected from:

4-hexyl-benzoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-yl methyl ester;

8-phenyl-octanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide;

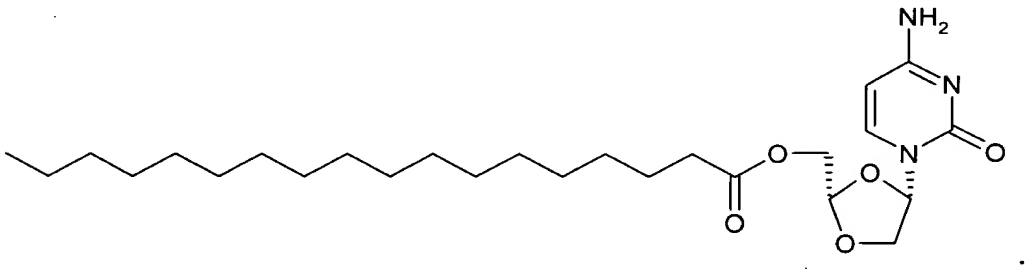
8-phenyl-octanoic acid 4-(4-amino-2-oxo-2H-pyimidin-1-yl)-[1,3]dioxolan-2-yl methyl ester;

4-pentyl-bicyclo[2.2.2]octane-1-carboxylic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-yl methyl ester;

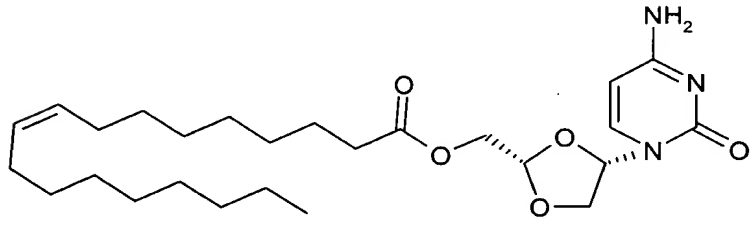
4-pentyl-cyclohexane-carboxylic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-yl methyl ester;

and mixtures thereof.

59. (Previously Presented): A compound according to claim 39, wherein the compound is



60. (Previously Presented): A compound according to claim 39, wherein the compound is



61. (Previously Presented): A compound according to claim 39, wherein the compound is octadec-9-enoic acid[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide.

62. (Previously Presented): A compound according to claim 39, wherein R_1 is H; C_{1-20} alkyl; C_{2-20} alkenyl; C_{6-10} aryl; C_{5-10} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Met, Cys, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} aryl, C_{7-11} arylmethyl, C_{2-7} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R_3 and R_4 are in each case independently H; C_{1-20} alkyl; C_{2-20} alkenyl; C_{6-10} aryl; C_{5-10} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NRH_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_6 is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-20} alkyl-C_{6-10} aryl, C_{0-20} alkyl-C_{5-10} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S; and

R_7 is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} aryl, C_{5-10} heteroaromatic ring, C_{3-20} nonaromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$.

63. (Previously Presented): A compound according to claim 39, wherein R_3 and R_4 are each H or R_3 and R_4 together can also be $=CH-N(C_{1-4}\text{-alkyl})_2$.

64. (Previously Presented): A compound according to claim 39, wherein R_3 and R_4 are each H.

65. (Previously Presented): A compound according to claim 39, wherein at least two of R_1, R_3 and R_4 are each H.

66. (New): A compound according to claim 39, wherein R_1 is C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S.

67. (Previously Presented): A compound according to claim 39, wherein R_1 is $-C(O)OR_6$ and R_6 is in C_{1-20} alkyl or C_{2-20} alkenyl.

68. (Previously Presented): A compound according to claim 64, wherein R_1 is $-C(O)OR_6$ and R_6 is in C_{1-20} alkyl or C_{2-20} alkenyl.

69. (Previously Presented): A compound according to claim 64, wherein at least one of R_1, R_3 and R_4 is $-C(O)OR_6$ and R_6 is in C_{1-20} alkyl or C_{2-20} alkenyl.

70. (Previously Presented): A compound according to claim 64, wherein at least one of R_3 and R_4 is $-C(O)OR_6$ and R_6 is in C_{1-20} alkyl or C_{2-20} alkenyl.

71. (Previously Presented): A compound according to claim 39, wherein R_1 is C_{5-10} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S.

72. (Previously Presented): A compound according to claim 66, wherein R_3 and R_4 are each H.

73. (Previously Presented): A compound according to claim 71, wherein R_3 and R_4 are each H.